INTERNATIONAL STANDARD

ISO 20069

First edition
2019-08

Guidance for assessment and evaluation of changes to drug delivery systems

Gestion des changements d'appareils dans les combinaisons de produits pour l'administration de médicaments

Reference number
ISO 20069:2019(E)

ISO copyright office
CP 401 • Ch. de Blandonnet 8
CH-1214 Vernier, Geneva
Phone: +41 22 749 01 11
Fax: +41 22 749 09 47
Email: copyright@iso.org
Website: www.iso.org

Published in Switzerland

Contents

Page

Foreword

ISO (the International Organization for Standardization) is a worldwide federation of national standards bodies (ISO member bodies). The work of preparing International Standards is normally carried out through ISO technical committees. Each member body interested in a subject for which a technical committee has been established has the right to be represented on that committee. International organizations, governmental and non-governmental, in liaison with ISO, also take part in the work. ISO collaborates closely with the International Electrotechnical Commission (IEC) on all matters of electrotechnical standardization.

The procedures used to develop this document and those intended for its further maintenance are described in the ISO/IEC Directives, Part 1. In particular, the different approval criteria needed for the different types of ISO documents should be noted. This document was drafted in accordance with the editorial rules of the ISO/IEC Directives, Part 2 (see www.iso.org/directives).

Attention is drawn to the possibility that some of the elements of this document may be the subject of patent rights. ISO shall not be held responsible for identifying any or all such patent rights. Details of any patent rights identified during the development of the document will be in the Introduction and/or on the ISO list of patent declarations received (see www.iso.org/patents).

Any trade name used in this document is information given for the convenience of users and does not constitute an endorsement.

For an explanation of the voluntary nature of standards, the meaning of ISO specific terms and expressions related to conformity assessment, as well as information about ISO's adherence to the World Trade Organization (WTO) principles in the Technical Barriers to Trade (TBT) see www.iso.org/iso/foreword.html.

This document was prepared by Technical Committee ISO/TC 84, *Devices for administration of medicinal products and catheters*.

Any feedback or questions on this document should be directed to the user's national standards body. A complete listing of these bodies can be found at www.iso.org/members.html.

Introduction

This document provides guidance to organizations wishing to implement a systematic approach to assess and evaluate changes to needle-based injection systems, needle-free injectors and aerosol delivery devices for medical use (see Clause 1) throughout their lifecycles. In particular, an organization can use the approach for changes to the drug delivery system from entry into pivotal or registration clinical studies through the end of commercial supply.

Due to the breadth of potential change circumstances, this document does not contain prescriptive technical requirements for assessing and evaluating drug delivery system changes but rather provides illustrative guidance for consideration.

This document does not replace or alter existing statutory and regulatory requirements for assessing drug delivery system changes.

Prior to using the process outlined in this document, the organization should have determined the objective of the change including the various opportunities/options for fulfilling the objective.

This document might also be useful for assessing and evaluating change to drug delivery systems other than needle-based injection systems, needle-free injectors and aerosol delivery devices for medical use.

The process can be applied to multiple product lifecycle stages, including design and development, production, storage and distribution, installation, servicing and final decommissioning/disposal of the drug delivery system or associated activities (e.g. up-dating of software). It can also be used by an organization's suppliers and external parties (e.g. raw materials, components, subassemblies, medical devices, sterilization services, calibration services, distribution services, maintenance services).

This document is not intended to replace or alter quality management systems, risk management, or usability engineering requirements in assessing these changes. Rather, it provides a common framework using a scientific and risk-based approach consistent with

— ISO 13485[4],

— ISO 14971[5], and

— IEC 62366-1[8].

Although this process focuses on user safety and drug delivery system performance, it also addresses lifecycle management and includes consideration of appropriate medicinal product guidance (e.g. ICH Q8, ICH Q9, ICH Q10 and ICH Q12). This will help assess the potential impact of changes on the quality, safety, and efficacy of the finished product for the target patient population.

Over the course of a finished product's lifecycle, there will be a broad array of drivers for change. These changes and their various design solutions can be motivated by, but are not limited to the following:

a) adverse event/complaint data;

b) voice of the customer, user feedback or market research;

c) usability studies;

d) changes in processes for production, production scale and supply chain logistics;

e) changes in material or source of supply;

f) impact of changes to the medicinal product that affect the drug delivery system.

This document provides examples of drug delivery system changes using a process flow (see Figure 1). These examples and the conclusions provided are purely illustrative and are intended to provide guidance on how to utilize this document.

It is the responsibility of organizations to provide evidence that the approach adopted is commensurate with the level of risk to ensure the quality, safety and performance of the drug delivery system. While the focus of this document is the changed drug delivery system, it is also possible that changes to the medicinal product might impact the drug delivery system (e.g. change in viscosity or volume of medicinal product resulting in changed drug delivery system performance). It is also possible that changes to the drug delivery system might impact the medicinal product (e.g. increased injection forces resulting in changed treatment). As such, one key aspect of this process is assessing the change for its potential impact on overall quality given the critical interface between the drug delivery system and the medicinal product. Organizations should evaluate potential impact to the medicinal product in accordance with relevant regulations and guidelines pertaining to medicinal products (e.g. ICH guidelines) to ensure the quality, safety and efficacy.

The core of this document is the process flow, which attempts to guide an organization through a risk-based approach based on drivers of change as mentioned above impacting the

— drug delivery system design,

— manufacturing process, and

— labelling and user interface.

The expectation is that such changes are evaluated through the risk assessment of how the change could impact system form, fit and function (including medicinal product flow paths) such that users are not negatively impacted in terms of quality, safety and performance of the drug delivery system. Given that a single change can affect more than one of the change types (e.g. a material change can also drive a process change), all change types should be assessed and evaluated.

The identification, analysis, evaluation and control of change are common regulatory requirements in the post approval phase of a product's lifecycle, but are also important in the clinical phase of development. Organizations should demonstrate that as the drug delivery system design evolves, the link between the drug delivery system and the medicinal product as tested in the clinical setting (for which market authorization is granted or is intended) is maintained.

Guidance for assessment and evaluation of changes to drug delivery systems

1 Scope

This document provides guidance for assessment and evaluation of planned changes to drug delivery systems that are integral with, packaged with, or cross-labelled for use with a specified medicinal product. This document is applicable to the drug delivery system's lifecycle from registration clinical studies to end-of-life. This document is applicable to the assessment of changes within the following drug delivery systems:

— needle-based injection systems for medical use;

— aerosol drug delivery devices;

— needle-free injectors for medical use.

NOTE These are covered by the ISO 11608 series, ISO 20072 and ISO 21649, respectively.

This document might also be useful for assessing and evaluate changes to other drug delivery devices or systems.

Examples of changes that are within the scope of this document include but are not limited to the following:

a) the same route of administration (e.g. change resulting in including a marketed prefilled syringe to an autoinjector);

b) changes to the drug delivery system design (e.g. change in configuration or layout of electrical and mechanical components);

c) changes to the medicinal product that affect the drug delivery system; including the primary container closure (e.g. viscosity, particle size);

d) changes in production or handling of the drug delivery system (e.g. process scale, manual to automated assembly, glue bond to sonic weld, mould cavitation, sterilization, storage, transportation, work instructions or methods);

e) changes in component materials or source of supply;

f) changes in software, including changes related to cybersecurity, encryption and connectivity;

g) changes in the user interface, including packaging;

h) changes to labelling and/or instructions for use.

Revisions or additions of software are within the scope of this document. The software can either be integrated into the physical drug delivery system, separate, or both.

The applicability of this document to non-integrated software is relevant to the extent that those software changes can impact the drug delivery system and/or impact how users interact with it.

Depending on the nature of the change, there can be additional assessments and resulting activities, which can be outside the scope of this document.

This document does not provide guidance for defining the objective of the change, nor the various potential opportunities/options for fulfilling this objective.

2 Normative references

There are no normative references in this document.

3 Terms, definitions and abbreviated terms

For the purposes of this document, the following terms and definitions apply.

ISO and IEC maintain terminological databases for use in standardization at the following addresses:

— ISO Online browsing platform: available at https://www.iso.org/obp

— IEC Electropedia: available at http://www.electropedia.org/

3.1 Terms and definitions

3.1.1
component
single item, or assembly of items (subassembly) within a *drug delivery system* (3.1.2)

3.1.2
drug delivery system
medical device or system whose primary purpose is the administration of a medicinal product such as drugs and biologics

Note 1 to entry: This term applies to combination of components and subassemblies of the system that are intended to be integrated with the medicinal product with the purpose of providing a method of administration of the medicinal product.

3.1.3
finished product
drug delivery system (3.1.2) and the medicinal product it is intended to deliver

Note 1 to entry: A finished product can be as a single integrated product combining both the drug delivery system and medicinal product as released by its manufacturer. It can also be a drug delivery system and medicinal product that are produced separately and integrated into its final, usable form by the end user.

Note 2 to entry: It is not intended to imply the status of a marketed product or manufacturing responsibility as defined by individual markets.

3.1.4
flow path
pathway the medicinal product or other liquid, gas or powder flow to the targeted site

3.1.5
organization
person or group of people that has its own functions with responsibilities, authorities and relationships to achieve its objectives

Note 1 to entry: The concept of organization includes, but is not limited to, sole-trader, company, corporation, firm, enterprise, authority, partnership, association, charity or institution, or part or combination thereof, whether incorporated or not, public or private.

Note 2 to entry: Regulatory bodies and others can use other terms for organization, such as manufacturer.

[SOURCE: ISO 9000:2015, 3.2.1, modified — the original Note 2 to entry was deleted and a new Note 2 to entry was added.]

3.1.6
quality
degree to which a set of inherent characteristics of an object fulfils requirements

Note 1 to entry: The term “quality” can be used with adjectives such as poor, good or excellent.

Note 2 to entry: “Inherent”, as opposed to “assigned”, means existing in the object.

[SOURCE: ISO 9000:2015, 3.6.2]

3.1.7
verification
confirmation, through the provision of objective evidence, that specified requirements have been fulfilled

Note 1 to entry: The objective evidence needed for a verification can be the result of an inspection or of other forms of determination such as performing alternative calculations or reviewing documents.

Note 2 to entry: The activities carried out for verification are sometimes called a qualification process.

Note 3 to entry: The word “verified” is used to designate the corresponding status.

[SOURCE: ISO 9000:2015, 3.8.12]

3.1.8
validation
confirmation, through the provision of objective evidence, that the requirements for a specific intended use or application have been fulfilled

Note 1 to entry: The objective evidence needed for a validation is the result of a test or other form of determination such as performing alternative calculations or reviewing documents.

Note 2 to entry: The word “validated” is used to designate the corresponding status.

Note 3 to entry: The use conditions for validation can be real or simulated.

[SOURCE: ISO 9000:2015, 3.8.13]

3.2 Abbreviated terms

ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
App	Application
BSE/TSE	Bovine Spongiform Encephalopathy/Transmissible Spongiform Encephalopathy
IFU	Instructions For Use
PK/PD	PharmacoKinetics/PharmacoDynamics
uFMEA	user Failure Modes and Effects Analysis
pFMEA	process Failure Modes and Effects Analysis
dFMEA	design Failure Modes and Effects Analysis
HFE	Human Factors Engineering
URS	User Requirements Specification
PRS	Product Requirements Specification

API	Active Pharmaceutical Ingredient
pH	potential of Hydrogen, a measure of acidity
cP	centiPoise, a measure of viscosity

4 Process

4.1 General

4.1.1 Process framework

The process outlined in this document provides a framework to assess and evaluate changes to a drug delivery system. It does not provide a framework to assess and evaluate changes to a medicinal product (e.g. reformulation driven by adverse event data). However, if the change to a medicinal product has the potential to impact the drug delivery system (e.g. reformulation increases viscosity impacting delivery forces), then the framework should be used to assess and evaluate the impact on the drug delivery system.

The process is initiated when a change has been proposed for potential implementation. Every change should be assessed based on the individual circumstances of the change. Where multiple changes are occurring simultaneously or concurrently, they should also be assessed for their ability to interfere with each other and/or to collectively impact the product in a manner different to their individual impacts.

The process should be divided into three phases as illustrated in Figure 1:

a) Phase A — Define and assess;

b) Phase B — Execute activities;

c) Phase C — Final evaluation.

Phase A, define and assess, starts with the thorough definition of the proposed change, i.e. the purpose with and scope for the proposed change, a change description including the current state and the proposed state after implementation. The next step is the identification of the change types based on the information collected in the definition step. The last step of this phase is an impact assessment on the performance, safety, stability, compatibility, process, usability, software, clinical data and regulatory compliance.

Phase B, execute activities, consists of two steps, the planning and the execution of the planned activities. During the planning step, all activities that need to be performed in order to prepare a proper implementation of the change should be determined. These activities can include but are not limited to design and development verification, design validation and process validation. The activities depend on the change type (see 4.2.2) and its associated risks and on the specific properties and requirements of the individual change and should be defined on a case by case basis. The planning step is concluded with the confirmation of readiness to perform the planned activities. In the execution step, all the planned activities are performed and completed, e.g. design and development verification work is conducted as per the verification plan established in the planning step. Completion of the activities is a prerequisite for change implementation and to enter the final evaluation Phase C of the change.

Phase C, final evaluation, includes an evaluation supporting a decision as to whether the change should be implemented based on the results obtained in Phase B.

As an organization proceeds through the process, knowledge and perspective obtained through the assessments (e.g. unacceptable risks, non-fulfilment of the objective or unforeseen difficulties in implementing the change) and/or changes in business needs (e.g. cost/time) can result in a decision to not proceed with the change. The basis for the decision should be documented.

Annex A provides an example of a template to guide the assessments and execution of the activities included in Figure 1. Annex B provides examples of completed templates.

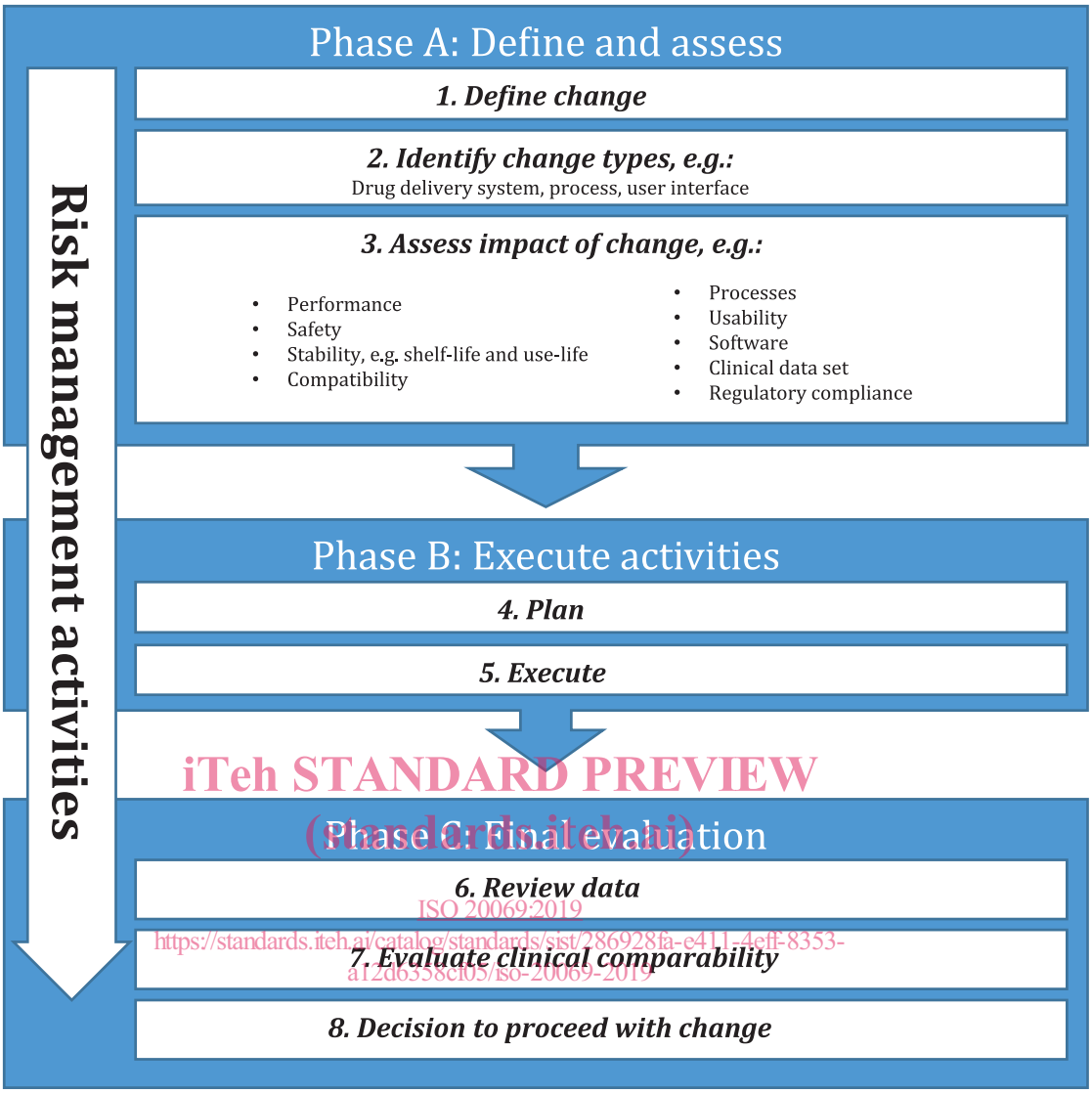

Figure 1 — Process flow for assessment and evaluation of changes to the drug delivery system

4.1.2 Quality and risk management

The process should be performed within the organization's quality and risk management system requirements. This process should be aligned with ISO 13485, in particular control of design and development changes. Risk assessment should be performed and risk controls should be implemented where needed in accordance with ISO 14971 during all phases of this process.

4.1.3 Relationships within the organization and with suppliers or external organizations

Due to the nature of drug delivery systems, it is common for separate functions within a single organization responsible for the drug delivery system to have responsibilities for different aspects of the finished product (e.g. formulation scientists responsible for the medicinal product aspects and device engineers responsible for the drug delivery system aspects). When there is a change to the drug delivery system, it is recommended to define internal roles and responsibilities for the change process and to establish a cross-functional team comprising the relevant levels and functions within the organization to be involved in each phase of this process.

Additionally, it is also common for one or more separate organizations to have responsibilities for different aspects of the product (e.g. component suppliers, medicinal product manufacturer and device manufacturer) and to work collaboratively. Where these relationships exist, it is essential to ensure

that roles and responsibilities with regards to notification of and approval of changes between the parties are defined. Quality agreements with suppliers and other external organizations are one way to ensure that changes that can impact the drug delivery system are transparent to the drug delivery system owner.

Depending on the intended application, changes made within the defined specification range can still be impactful for the drug delivery system. For example, shifting the nominal, as an improvement, within the acceptable range for a particular attribute (e.g. silicone level) can impact the functionality of an injection device. The assessment of this change from a supplier can have no impact as the component still meet specification, but could result in a change in drug delivery system functionality.

4.2 Phase A — Define and assess

4.2.1 Define change (Figure 1, box 1)

This process is about defining the objective for the change and providing a description of the change with the appropriate details. It can also be useful to identify what is not changing (e.g. no change to the primary container and medicinal product flow path).

An objective for the change can include but is not limited to improved safety, improved performance, or substitution of a component.

4.2.2 Identify change types (Figure 1, box 2)

The "current state" and "proposed state" of the drug delivery system as a result of the change should be described. The change types should be identified based on the specifics of the change. The assessments in Table A.1 can be useful to perform the preliminary change type identification.

Given that a single change can fall under more than one of the change types (e.g. a material change can also be a process change), it should be assessed whether the change is included in each of the change type categories to ensure an assessment.

Change types that should be identified include, but are not limited to the following:

a) **Materials**: Change of material of the drug delivery system components or its packaging including, but not limited to, type, grade, chemistry, formulation, additives, colorants, supplier/sub-suppliers, manufacturing materials and/or processing aids.

b) **Form and fit**: Change in physical attributes, such as component dimensions relative to interface/interaction with other components and sub-assemblies.

c) **Function**: Change in system function as defined in the design input requirements and associated design specifications (e.g. dose accuracy, environmental and mechanical robustness, functions that support label claims such as deliverable volume).

d) **Process change**: Change in processes for production and handling of the drug delivery system. Process changes include, but are not limited to changes to the component manufacture, sub-assembly and system assembly processes including the following: process control, packaging, different production sites, sterilization, environmental conditions and storage.

e) **User interface change**: Change impacting the user interface. User interface changes include, but are not limited to changes to the user population, intended users, form factor, packaging, labelling, instructions for use, software, printed materials and training.

f) **Software**: Change to embedded or connected software, including change of separate software that relates to the use of the drug delivery system (e.g. dosing app).

g) **Medicinal product**: Change to the medicinal product that can impact the drug delivery system.

4.2.3 Assess impact of change (Figure 1, box 3)

An assessment should be performed to identify potential impact to design inputs, user requirements and risk control measures to determine whether verification and/or validation activities are required to implement the change. Table A.2 can be a helpful guide when assessing impact of key areas (e.g. performance, shelf-life, clinical evaluation, etc). Based on the assessment, additional verification and/or validation studies should be planned.

For areas that could be potentially impacted by a change, it should be assessed whether existing evidence is adequate to support the change. The assessment should include a review of best available information and objective evidence (data, modelling, literature, etc.).

It should be considered whether the change has the potential to fulfil the objective(s), to cause any new hazard(s), or has the potential to modify the established risk profile and/or the performance of the drug delivery system. Changes should be assessed in relation to potential impact, direct and indirect, on each of

a) the drug delivery system,

b) the medicinal product,

c) the users,

d) manufacturing systems, and

e) compliance with applicable statutory and regulatory requirements.

The assessments should identify required updates of the design and development documentation for the drug delivery system, including, but not limited to drawings, 3-D models, other specifications, software, electronics, hardware, tolerance stack-ups, test equipment, test methods and operating parameters.

4.2.3.1 Assess drug delivery system performance

The drug delivery system performance should be assessed for each type of drug delivery system change. Existing drug delivery system design input requirements should be assessed in order to determine which requirements might be affected or added due to the change. The functional robustness should be assessed – including robustness to shipping, aging, drop, shock, etc.

It should be assessed whether a physical change relates to surfaces that contact the medicinal product liquid or air (in the case of inhaled products). Changes to surface treatments and physical attributes of the drug delivery system components should also be assessed for potential impacts to performance.

A medicinal product change that can potentially impact how the drug delivery system performs should be assessed.

Changes to the interface/interaction with other system components, e.g. sub-assemblies, needles, spacers, primary packaging such as container closures and blisters, and/or other changes of parts/components included in the drug delivery system, should be assessed.

4.2.3.2 Assess safety

It should be assessed whether the change has an impact on the safety of the finished product. Assessments should include, but are not limited to, electrical safety, mechanical safety, biocompatibility, BSE/TSE, material composition (such as whether the material is made with natural rubber, latex, etc.), as appropriate based on the design inputs for the product. Sterility performance should be considered, if applicable.

If the changed material has contact with the medicinal product's flow path, its impact on the quality, safety and performance of the drug delivery system and the quality, safety and efficacy of the medicinal product should be assessed. It should also be assessed whether the material is permitted by applicable